

ORAL SUBMUCOUS FIBROSIS- AN OVERVIEW

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ABSTRACT

OSMF is a chronic condition of the oral cavity which results in permanent disability. The pathogenesis is poorly understood and the disease is difficult to treat. OSMF is associated with immunological changes (altered levels of serum immunoglobulins) and the effect of treatment (especially antioxidants and levamisole) on serum Ig is not known.

KEYWORDS: Oral Submucous Fibrosis (OSMF), Oral Fibrosis

INTRODUCTION

Oral submucous fibrosis is a chronic disease of insidious onset featuring the deposition of fibrous tissue in the submucous layer of the palate, fauces, cheek, lips, pharynx and esophagus. The underlying muscles of mastication may be affected resulting in trismus and disability.¹

OSMF was defined by Pindborg and Sirsat as “*an insidious, chronic disease affecting any part of the oral cavity and sometimes the pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxtaepithelial inflammatory reaction followed by fibroelastic change of the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to eat.*”²

HISTORICAL ASPECT

In as early as 600 BC, Sushruta described a condition called Vidari which resembled OSMF and had features of progressive narrowing of the mouth, depigmentation of the oral mucosa and pain on taking food.³

In modern literature, OSMF was first described by Schwartz in 1952, in five Indian women from Kenya. He named the condition Atrophie Idiopathica (Tropica) Mucosae Oris. In India, Joshi described the disease for the first time in 1953 and named it submucous fibrosis of the palate and pillars. Subsequently various other authors reported their cases and other names that were suggested are diffuse oral submucous fibrosis, idiopathic palatal fibrosis and sclerosing stomatitis. Pindborg and Sirsat suggested the term juxtaepithelial fibrosis.⁴

PREVALENCE

Since its first description by Schwartz in 1952, OSMF has been seen more commonly in people of Indian origin. No religion or caste is specifically affected.

In the 1960s the following prevalence figures were observed in 35,000 Indians visiting dental colleges- Lucknow 0.5 %, Bombay 0.7 %, Bangalore 0.2 % and Trivandrum 1.2%.⁵ In 1968, a survey was conducted among 50,915 villagers to know the prevalence of OSMF in rural India and the prevalence figures were-Gujarat 0.2%, Kerala 0.4 %, Andhra Pradesh 0.04%, Singhbhum 0% and Darbhanga 0.7 %.⁶

The prevalence of OSMF in the Indian population in South Africa was between 0.5% - 1.2%.⁷ In 2002, the statistics of OSMF for India alone was 5 million people.⁸ The disease has also been reported among local population in Sri Lanka, Myanmar, Singapore, Thailand, China, South Vietnam, Fiji, Papua New Guinea, and Saudi Arabia and sporadically among Europeans.⁹

AGE

OSMF occurs over a wide age range. Majority of the patients diagnosed with OSMF are between the ages 20-40 years.¹⁰

SEX

Reports of sex ratio vary, but seem to favor a female predominance.

In a study to evaluate regional variations in OSMF undertaken in Ernakulam and Pune, 72% of the patients were females in Ernakulam and 46 % in Pune.¹¹ In a study comprising 44 subjects of Asian origin in UK, the female to male ratio was found to be 4.5:1.¹²

ETIOLOGY

The etiology of OSMF is obscure. From current data it is clearly evident that the disease is multifactorial, as is the case with oral cancer and most of the other precancerous lesions. Till date no conclusive evidence has been found despite investigations on factors implicated in the development of OSMF which includes local factors- chilli, areca nut and misri; and systemic factors-nutritional deficiency, genetic predisposition and autoimmunity.

Chilli

OSMF is found more commonly among Indians. A common inability to tolerate food seasoned with chillies (*Capsicum annum* and *Capsicum frutescens*) in patients with OSMF led to the hypothesis that the disease is due to some form of hypersensitivity to capsaicin, the irritant in chillies.

To verify this, capsaicin was applied topically to palates of Wistar rats. A limited connective tissue response was seen in the normal healthy animals, but the reaction was enhanced in protein or vitamin deficient animals. The investigators concluded that chilli was not the sole causative agent because the microscopic alterations seen were non specific and indicated only a reaction to the irritant.¹² Similar results could not be reproduced in hamster cheek pouch experiments.¹³

Areca Nut

The use of areca nut is thought to be the most important causative factor. Areca nut is the endosperm of the fruit of the areca catechu palm. The fruit is orange yellow when ripe. After removing the fibrous pericarp from the seed or endosperm, it is used fresh after sun drying or in a cured form.

Contents of an Areca Nut

- Tannins- 11.4%- 26%

Gallotannic acid- 18.03%

D Catechol- 0.4%

- Alkaloids 0.15%-0.67%

Arecoline is most abundant; arecaidine, guvacine and isoguvacine, arecolidine and guvacoline are also present in small quantities.

- Other substances comprise fats, carbohydrates and proteins.¹⁴

In India areca nut is chewed by itself in the form of various areca nut preparations-scented supari, mawa, mainpuri tobacco, pan masala and in betel quid with or without tobacco. In Taiwan, two halves of betel nut are sandwiched with a piece of inflorescence of *Piper betle* and lime paste and chewed with or without *Piper betle* leaf.⁴⁰ Areca nut chewing is practiced in various forms in several countries in south East Asia, Oceania, the Pacific islands and by Indian emigrants living abroad.

Areca nut chewing is strongly associated with OSMF. A high correlation has been found in Taiwan between areca nut chewing and oral submucous fibrosis.¹⁵

In vitro studies have shown that arecoline and arecaidine stimulate proliferation of fibroblasts and enhance the synthesis of collagen.^{16, 17}

Misi

Misi is a black colored powder that is used more commonly by women in rural areas of Uttar Pradesh. It contains washing soda, borax, charcoal of myrobalan, and fuller's earth in varying proportions. Misi is used as a cosmetic to keep the teeth shiny and clean. These substances are thought to be a causative factor of OSMF among these women.¹⁸

Nutritional Deficiencies

Several investigators have reported nutritional deficiencies in patients with OSMF. The serum total protein and albumin level, hemoglobin and serum iron in OSMF patients have been found to be significantly lower than in normal patients. In the same study it was found that total iron binding capacity was elevated and the percentage saturation of transferrin was significantly lower.¹⁹

Genetic Predisposition

Although betel nut chewing is widely practiced in some geographical regions, only a minority of genetically predisposed individuals are susceptible to OSMF. The frequency of HLA antigens and haplotypic pairs in patients with OSMF and ethnically matched non consanguineous controls was investigated. The haplotypic pairs A10/DR3, A10/B8 and B8/D3 showed an increased frequency in the patients, but the latter two were not statistically significant.²⁰ In South Africa, HLA typing was carried out on OSMF patients of Indian origin. The HLA antigen patterns as reported by Cannif et al²⁰ were not encountered in patients with oral submucous fibrosis or in persons practicing the betel habit without the disease. However, it was also noted that there were inconsistencies in the presentation of the disease, with some patients having severe OSMF associated with a short duration of the betel habit and a low frequency. In Taiwan, a significant increase in HLA phenotype B76 and haplotype pairs of HLA-B52/CW7, B62/CW7 and B48/CW7 was seen.²¹

All these studies suggest that some subjects with particular HLA haplotypes are more prone to develop OSMF.

Autoimmunity

Several characteristics indicate that OSMF may be an autoimmune disease:

A high incidence of autoantibodies has been reported in Taiwanese subjects with OSMF. This study demonstrated a significantly higher positive ANA (23.9%), SMA (23.9%), and GPCA (14.7%) in OSMF patients compared to healthy controls (9.2%, 7.3%, 5% respectively) which is suggestive of OSMF being an autoimmune condition.²¹

More recently, investigators have thrown light on the role of cytotoxic T lymphocyte associated antigen 4 (CTLA-4) in OSMF. Patients with OSMF have a higher frequency of the G allele at position +49 on exon 1 of CTLA-4 compared with controls. CTLA-4 polymorphism has also been associated with certain autoimmune diseases such as SLE, IDDM, Graves' disease, Hashimoto thyroiditis, multiple sclerosis and rheumatoid arthritis.²²

PATHOGENESIS

The pathogenesis of OSMF is believed to be multifactorial. Factors that trigger the disease include consumption of chillies, chewing areca nut, nutritional deficiencies, and immunologic processes. The most important risk factor however is the chewing of betel quid (containing areca nut, tobacco and lime) and this has been supported by epidemiologic studies as well.

In iron deficiency anemia the oral epithelium becomes atrophic with reduced maturation compartment but an increased keratin compartment. Cell kinetics have shown an increased cell production indicating that despite atrophy, the epithelial turn over is rapid. From this it can be presumed that there may be increased susceptibility to chemical carcinogens due to an increased population of dividing cells and also to a more permeable epithelium, leading to development of oral precancer including OSMF.²³ Decrease in the levels of iron and ascorbate has been reported in patients with OSMF. However, formation of collagen requires ferrous iron and ascorbic acid. The decreased plasma ascorbate and iron levels may be due to their utilization in the fibrosis process.²⁴

Betel quid is a source of constant irritation to oral tissues when present in the mouth. Several betel quid constituents [arecoline, (+)-catechin] and extracts of inflorescence of piper betel and betel nut have been found to decrease cell survival and proliferation in a dose dependant manner in human buccal mucosal fibroblasts. The extracts also induce DNA strand breakage in a dose dependant manner suggesting that they act as cytotoxic and genotoxic agents.²⁵ Betel nut extracts also have the ability to stimulate cell proliferation and might act synergistically on the pathogenesis of OSMF and oral cancer.

OSMF is considered to be a collagen metabolic disorder. At the molecular level the collagen production and collagen degradation are regulated by transforming growth factor-beta (TGF- β) and the flavonoids present in areca nut.

There are three main events modulated by TGF- β , which favor collagen production:

- Activation of procollagen genes.
- Elevation of procollagen proteinase levels
- Upregulation of lysyl oxidase (LOX) activity.

The transcriptional activation of procollagen genes by TGF- β causes an increased expression of procollagen genes and hence contributing to increased collagen level in OSMF. N- and C- procollagen proteinases play an important role in processing procollagen into collagen fibrils. LOX is dependant on copper and is an essential enzyme for final processing of

collagen fibers into a stabilized, covalently cross linked mature fibrillar form that is resistant to proteolysis. Areca nuts have been shown to have a high copper content. Trivedy et al have reported a high copper content in oral tissues of patients with OSMF.^{26,27} Copper has been implicated in tissue fibrogenesis via the copper dependant enzyme lysyl oxidase (LOX) which has a crucial role in the cross linking of collagen and elastin fibers. LOX has also been implicated in other fibrotic disorders such as hepatic and pulmonary fibrosis and scleroderma.²⁸

Collagen Degradation Pathway

There are two main events modulated by TGF- β which decreases collagen degradation-

- Activation of tissue inhibitor of matrix metalloproteinases gene (TIMPs).
- Activation of plasminogen activator inhibitor (PAI) gene.

Matrix metalloproteinases (MMPs) are a set of structurally related matrix proteases. TIMPs are specific inhibitors of MMPs and control their local activities in tissues. An increased expression of TIMPs has been reported in oral tissues of patients with OSMF by Chang et al²⁸ and Sheih et al.²⁹ TGF- β activates TIMP gene which increases the tissue level of TIMPs. The TIMPs inhibit activated collagenase thereby decreasing collagen degradation. Type 1 plasminogen activator inhibitor is a 50kDa glycoprotein belonging to the serine protease superfamily. Plasminogen activators and their inhibitors are thought to play a key role in the balance of proteolytic and anti proteolytic activities that regulate matrix turnover. Yang et al in their study demonstrated that arecoline was capable of stimulating PAI 1 mRNA, and PAI 1 expression was elevated in OSMF specimens compared to normal buccal mucosa. TGF- β activates PAI genes which increase synthesis of PAI; PAI inhibits conversion of plasminogen to plasmin which decreases collagen degradation.³⁰

Another explanation of fibrosis is that chewing areca nut leads to muscle fatigue. Over activity of the muscle results in excessive glycogen consumption, leading to glycogen depletion. The increased muscle activity and diminished blood supply following connective tissue changes owing to extensive OSMF leads to degeneration and fibrosis of the muscle.³¹

The collagen that is synthesized is mostly insoluble and in cross linked form. Besides stimulating fibroblast proliferation and collagen synthesis, areca nut alkaloids are also thought to inhibit fibroblast phagocytosis which leads to fibrosis. Tsai et al investigated phagocytosis of collagen and fibronectin coated beads by fibroblast cultures in the presence of areca nut alkaloids with an in vitro model system. They found that arecoline and arecaidine caused a dose dependant inhibition of phagocytosis.³² Thus OSMF lesions appear to contain fibroblasts with marked deficiencies in collagen and fibronectin phagocytosis. The flavonoids tannin and catechin render the collagen fibers resistant to degradation by stabilizing the collagen fibers.

Oral submucous fibrosis may affect persons of any age and sex. No caste or religion is specifically affected. It has a slow and insidious onset. It may take two to five years for the disease to become clinically apparent. Any site in the oral cavity may be involved.

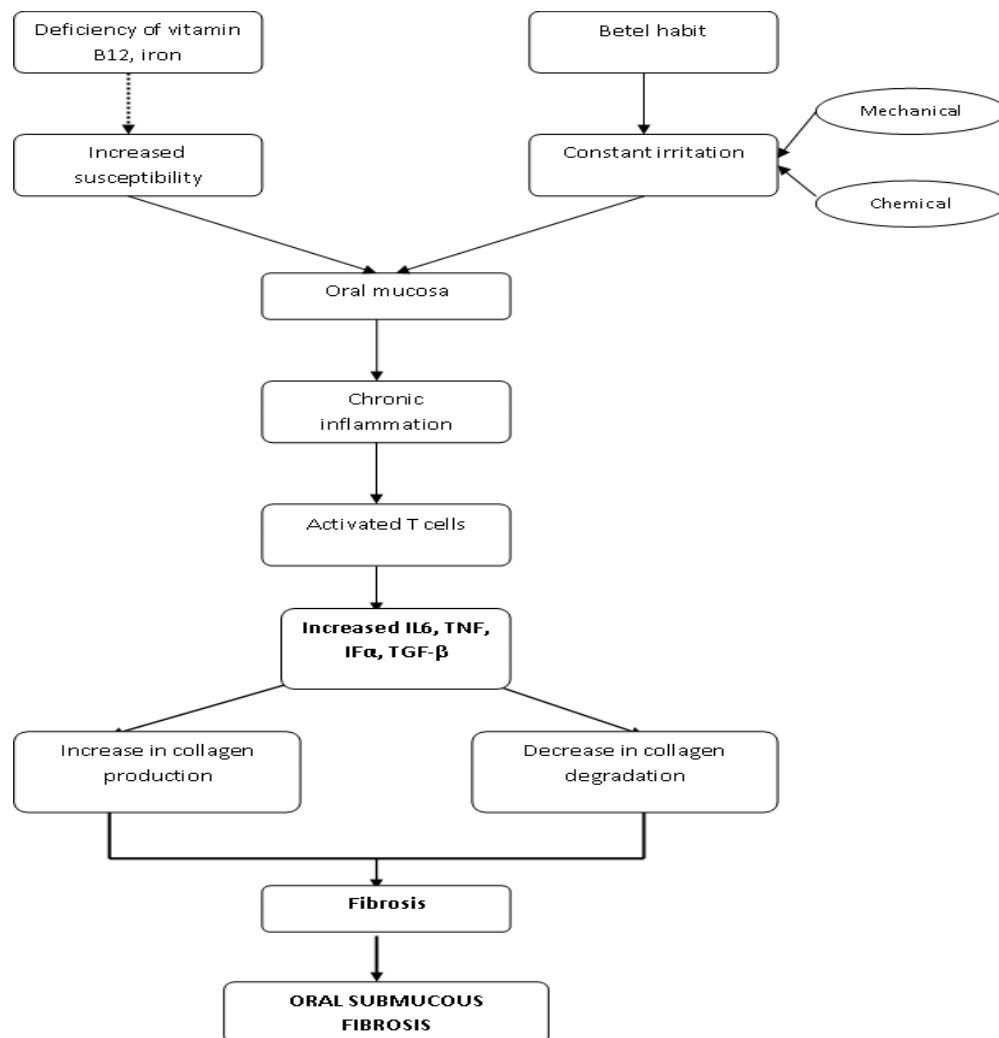


Figure 1

CLINICAL FEATURES

Symptoms

Early Symptoms

The early symptoms include burning sensation. The burning sensation is usually present only while eating spicy food. This is accompanied by an increased salivation. Some patients may have an itching sensation as reported by Bhatt and Dholakia³³ which is probably due to release of histamine from mast cells.

Late Symptoms

As the disease progresses, there is a gradual increase in stiffening of the oral tissues. The patients start experiencing increasing difficulties in chewing, swallowing and speaking and most consistently complain of inability to tolerate even non spicy food.³⁴ The deposition of collagen fibers around the minor salivary glands and salivary gland ducts leads to xerostomia in later stages. As the disease progresses there is dysphagia, restricted mouth opening, restriction in tongue protrusion and cheek flexibility.³⁵ Patients may rarely complain of nasal regurgitation or nasal intonation to their speech. Defective gustatory function has been reported in these patients, which may be due to reduced contact surface of the tongue mucosa while chewing, atrophy of taste buds, or perineural fibrosis. There may be earache and relative loss of auditory acuity due to stenosis of the opening of the eustachian tube.³⁶

SIGNS

Early Signs

The early signs of the disease are a mild to moderate blanching of the oral tissues. Fibrosis may not be evident, or they may be seen arching from the anterior faucial pillars into the soft palate as a delicate reticulum of interlacing white strands which later become confluent. Slight rigidity may be felt in the oral tissues in the early stages and the bands are diffuse and mild in the early stages. The occurrence of vesicles has been reported in some patients in the early stages of the disease which later form ulcers.³⁷

Late Signs

Gradually, as the disease progresses the mucosa gets a mottled or marble like appearance where dense pale areas alternate with areas of normal appearing mucosa or areas of melanin pigmentation. Occasionally fiery red areas appear. Appearance of petechiae has been reported in some cases. As the disease progresses, thick fibrous bands appear in the submucosal layer of the oral soft tissues. The fibrous bands run vertically in the buccal mucosae, and horizontally on the soft palate and rima oris. The bands become dense and confluent causing rigidity and stiffness of the oral tissues leading to restricted movement. Deposition of fibrous bands in the cheeks causes flattening of the cheeks. Recurrent ulceration may be present due to repeated trauma to the buccal mucosa from rubbing against buccal surfaces of the teeth. The fibrosis is usually bilateral. When there is unilateral involvement, fibrosis of pterygomandibular raphe on the affected side may produce mandibular deviation in later stages.

Circular bands may be palpable around the lips causing them to appear thin or distorted. The faucial pillars become short, thick and extremely hard. Tonsils become pressed between the pillars and appear blanched. When the soft palate is involved, the bands radiate from the median raphe to the anterior faucial pillars. The voice becomes nasal and the uvula shrunk and bud like, and mobility is restricted. Sometimes fibrosis may spread down to involve the pharynx and pyriform fossa. Fibrosis of the tongue is less advanced than the buccal mucosa or the lip and is associated with reduced mobility of the tongue. Papillary atrophy is present in later stages. The floor of the mouth is blanched and leathery; the gingiva is fibrotic, depigmented and devoid of its normal stippled appearance. A marked reduction has been seen in buccal and lingual vestibular sulci.³⁷

STAGING OF OSMF

Various authors have divided OSMF into different stages based on the degree of limitation of mouth opening, distribution of fibrous bands, cheek flexibility, and tongue protrusion.

II. Gupta DS, Gupta MK, Golhar BL clinically classified OSMF into four stages as per the increasing intensity of the trismus;³⁸

Very Early Stage: The patients complain of burning sensation in the mouth or ulcerations without difficulty in opening the mouth.

Early Stage: Along with symptoms of burning sensation patients complain of slight difficulty in opening the mouth.

Moderately Advanced Stage: The trismus is marked to such an extent that the patient cannot open his mouth more than two fingers width. Patients therefore experience difficulty in mastication

Advanced Stage: Patient is undernourished, anemic and has marked degree of trismus and/or other symptoms as mentioned above.

III. Bailoor DN clinically staged OSMF into three stages with values taken from the study done by Mathur RM, Jha T (1993)³⁹

Stage 1: Early OSMF

- Mild blanching.
- No restriction in mouth opening. The mouth opening is measured from the mesioincisal angle of the upper incisor and the lower central incisor of the same side. The normal values are - Males-5.03 cm, Females-4.5 cm
- No restriction in tongue protrusion: Measured from mesioincisal angle of upper central incisor to the tip of the tongue when maximally extended with mouth wideopen. The normal values are -Males-6.73 cm, Females -6.07 cm.
- Cheek flexibility, CF = V1-V2

V1-Two points measured between at one third the distance from the angle of the mouth on a line joining the tragus of the ear and the angle of the mouth, the subject is then asked to blow his cheeks fully and the distance measured between the two points marked on the cheek.

V2-The patient is then asked to release the air and the distance between the two points is measured at rest.

Mean value for males- 1.2 cm, females- 1.08 cm.

- Burning sensation only on taking spicy food, or hot temperature liquids, etc.

Stage 2: Moderate OSMF

- Moderate to severe blanching.
- Mouth opening reduced by 33%, tongue protrusion reduced by 33%, flexibility also demonstrably decreased.
- Burning sensation even in absence of stimuli.
- Palpable bands felt.
- Lymphadenopathy either unilateral or bilateral.

Demonstrable anemia on hematological examination.

Stage 3: Severe OSMF

- Burning sensation very severe. Patient unable to do day to day work.
- More than 66% reduction in the mouth opening, cheek flexibility and tongue protrusion. In many the tongue may appear fixed.
- Ulcerative lesions may appear in cheek.
- Thick palpable bands.
- Lymphadenopathy bilaterally evident.

IV. Haider SM et al studied 325 patients suffering from OSMF. The purpose of study was to stage the severity of the disease (functional staging) using an objective measure (inter-incisal opening) and to study its relationship to clinical staging. They staged the disease clinically and functionally as follows⁴⁰:

Clinical Stage

- Faucial bands only.
- Faucial and buccal bands.
- Faucial, buccal, and labial bands.

Functional Stage

- Mouth opening ≥ 20 mm.
- Mouth opening 11-19 mm.
- Mouth opening ≤ 10 mm.

HISTOPATHOLOGY

Histological changes in cases of OSMF can be dealt with under following headings.

- Changes in the epithelium.
- Changes in subepithelial tissue.

Changes in the Epithelium

The epithelial changes in oral submucous fibrosis have been variously described by different authors as normal epithelium with flattening of the rete pegs; acanthosis and parakeratosis; marked thickening and acanthosis; hypertrophic epithelium with occasional areas of atrophy and liquefaction of the basal layer; normal but somewhat atrophic epithelium and thickened squamous epithelium with deep invaginations of rete pegs into the lamina propria.

Increased mitotic activity and coexistent squamous cell carcinoma has also been reported in biopsy specimens. A marked reduction in melanin pigment in the basal cell layers has been seen which apparently has been displaced into the upper part of lamina propria where it accumulates in clumps.⁴¹

Changes in Subepithelial Tissue

- A marked epithelial atrophy has been reported by many authors and it is suggested that marked atrophy of the epithelium is probably due to changes in the underlying epithelium namely fibroelastic transformation of the lamina propria, and hyalinised tissue around the blood vessels resulting in reduced nutrition to the epithelium and atrophy.⁴¹
- Four consecutive stages, based upon sections stained with hematoxylin and eosin, have been described in connective tissue in patients with OSMF⁴¹

The Very Early Stage

Characterized by a finely fibrillar collagen, dispersed with marked edema. The fibroblastic response is strong, with plump young cells containing abundant cytoplasm. The blood vessels are sometimes normal, but more often they are dilated and congested. Inflammatory cells mainly polymorphonuclear leukocytes with occasional eosinophils are present.

The Early Stage

The juxta-epithelial area shows early hyalinization. The collagen is still seen as separate bundles, which are thickened. Plump young fibroblasts are present in moderate numbers. The blood vessels are often dilated and congested. The inflammatory cells are mostly mononuclear lymphocytes, eosinophils, and occasional plasma cells.

The Moderately Advanced Stage

Collagen is moderately hyalinized. The amorphous change starts from the juxta-epithelial basement membrane. Occasionally, thickened collagen bundles are still seen separated by slight residual edema. The fibroblastic response is less marked, the cells present being mostly adult fibrocytes with elongated spindle shaped nuclei and scanty cytoplasm. Blood vessels are either normal or constricted as a result of increased surrounding tissue. The inflammatory exudate consists of lymphocytes and plasma cells, although occasional eosinophils are seen.

The Advanced Stage

The collagen is completely hyalinized and is seen as a smooth sheet, with no separate bundles discernible. Edema is absent. The hyalinized areas are devoid of fibroblasts, although a thin, elongated cell or vestigial nucleus is seen at rare intervals along the fiber bundle. Blood vessels are completely obliterated or narrowed. The inflammatory cells are lymphocytes and plasma cells.

Apart from connective tissue repair process, vascular response due to inflammation has been very commonly found in OSMF. Normal dilated and constricted blood vessels, often in combination, have been observed in the same section. The melanin containing cells in the lamina propria become surrounded by dense collagen, which explains the clinically observable loss of pigment. Metachromatic areas are also observed. A rise in mast cells occurs in the earlier stages of the disease, but in more advanced cases the counts are similar to those seen in normal mucosa or even lesser.⁴²

PRECANCEROUS NATURE AND MALIGNANT TRANSFORMATION

The possible precancerous nature of OSMF was first described by Paymaster in 1956 when he observed slow growing squamous cell carcinoma (SCC) in one third of the cases of OSMF.⁴³

In an observation of biopsy specimens from OSMF patients, Pindborg found hyperchromatism, increased mitotic activity, and shift in nuclear: cytoplasmic ratio. To substantiate the precancerous nature of the condition he listed five criteria:

- High occurrence of oral submucous fibrosis in patients with oral cancer.
- A higher incidence of oral cancer among patients with oral submucous fibrosis.
- Histologic diagnosis of oral cancer without any clinical suspicion among oral submucous fibrosis cases.
- High frequency of epithelial dysplasia.
- Higher prevalence of leukoplakia among OSMF cases.

Pindborg et al reported a malignant transformation rate of 4.5% in 66 oral submucous fibrosis patients during a follow up period of 4-15 years.⁴⁴

TREATMENT

Oral submucous fibrosis is a premalignant condition with debilitating consequences. Till date there is no report

suggesting spontaneous regression and no widely accepted treatment protocol exists for the treatment of oral submucous fibrosis, although various approaches have been tried. Medical, surgical modalities and physiotherapy have been tried with varying results, but the relief from symptoms does not seem to be permanent. Appropriate management begins with patient education regarding the ill effects associated with the habit of areca nut chewing, tobacco and pan, and motivation to quit the habit. It should also be made clear to them that the disease is irreversible despite quitting that areca habit and is associated with development of cancer.

The management of OSMF can be classified into the following categories:

Medical Management: The various pharmacologic approaches that have been tried include:

- Micronutrients/Antioxidants
- Intralesional injections
- Arsenotyphoid injections
- Corticosteroids-dexamethasone, triamcinolone acetonide
- Placental extracts
- Hyaluronidase, chymotrypsin
- IFN γ
- Peripheral vasodilators

Alternative Medicine - Immune milk

- **Physiotherapy**
- **Surgical treatment**

Medical Management

OSMF is associated with an impaired nutrition status; therefore some investigators have tried supplementing *multiple micronutrients* in patients with OSMF. Kumar et al treated 82 patients with OSMF for twelve weeks. They divided the patients into five groups. Patients in group A were treated with 50,000 IU of vitamin A, group B vitamin A 50,000 IU with zinc sulphate 220 mg TDS, group C- zinc sulphate 220 mg TDS, group D zinc sulphate 220 mg TDS with intralesional hydrocortisone 4 mg/ week and group E- intralesional hydrocortisone 4mg/week. It was found that supplementation of oral zinc either alone or in combination with vitamin A or corticosteroid was beneficial in the treatment of OSMF.⁴⁵

Treatment of OSMF with daily supplementation of a *combination of vitamins* (A,B-complex,C,D,E) and minerals (iron, calcium, copper, zinc, manganese and others) has shown a significant symptomatic improvement in tolerance to spices and extent of mouth opening. However improvement with regard to symptoms such as referred pain and burning sensation and ulceration did not reach statistical significance. A significant proportion of concomitant lesions like leukoplakia also regressed. The study indicated that improvements in symptoms and signs of OSMF could be achieved with multiple micronutrient supplementations.⁴⁶

Administration of *nutrient antioxidants* to patients with OSMF may have a protective effect along with clinical improvement. Gupta et al treated 6 cases of OSMF with a pharmacological preparation containing beta carotene 50mg,

vitamin A palmitate 2500 IU, vitamin E acetate, 10 IU with vitamin C, zinc, copper and manganese (ANTOXID capsules). Improvement was seen in the symptoms in all the patients.⁴⁷

A comparative study was conducted by Borle et al on OSMF patients. They were divided into two groups, and group one was treated with *injections of triamcinolone* 10mg/ml diluted in 1 ml of 2% lidocaine with *hyaluronidase* 1500 IU, biweekly for 4 weeks. Group two was given 50,000 IU of *vitamin A* in the form of chewable tablets once daily, *oral ferrous fumarate* tablets 200mg daily and *topical betamethasone* drops (0.5mg/ml) every 6 hours for 3 weeks. The burning sensation disappeared but there was no improvement in trismus. The disease got reactivated after 3-4 months.⁴⁸

Intralesional injections of corticosteroids (dexamethasone) and hyaluronidase in combination or singly for a period of ten weeks has provided relief from symptoms such as burning sensation, painful ulceration, and trismus, and signs of OSMF namely blanching, suppleness and fibrous bands. In a comparative study by Kakar et al, patients with OSMF were divided into four groups and treated for ten weeks-group one was given dexamethasone 4mg biweekly, group two was given hyaluronidase 1500 IU with 2% Lignocaine, group three was given both dexamethasone and hyaluronidase, and group four was given placental extracts intralesionally. They found that the combination treatment showed better results than that in the other three groups.^{49, 50}

Placental extracts act biogenic stimulants by stimulating metabolic and regenerative process thereby favoring recovery. Weekly intralesional injections for a month or till symptoms subside have shown significant relief from burning sensation, and significant improvement in trismus, color of the mucosa, reduction of fibrous bands. The improvement in tongue protrusion was not significant. Follow up of patients treated with placental extracts has shown that the improvement is sustained.^{51, 52}

Gupta and Sharma treated their patients with injections of *chymotrypsin*, *hyaluronidase* and *dexamethasone* either alone or in combination. Significantly better results were obtained when all three were combined together.⁵³

IFN γ is proposed to downregulate fibroblast proliferation and collagen synthesis and upregulate antifibrotic cytokine and collagenase synthesis. These injections when given intralesionally in keloids and hypertrophic scars have resulted in clinical improvement. When intralesional IFN γ was tried in OSMF patients there was a reduction in burning sensation, increased suppleness of the mucosa, and mouth opening. Each patient received intralesional injection of 0.25 ml (50 mg) of IFN- γ after application of EMLA (Eutectic Mixture of Local Anesthetics) local anesthetic cream for 15 minutes, twice a week over 8 weeks, giving a total of 15 injections. Mouth stretching for each patient was also done with an adapted chemistry clamp three times a day for 15 minutes.⁵⁴ Sharma et al used *nylidrin hydrochloride (in the form of tablets)*, a *peripheral vasodilator* along with conventional therapies vitamin A, E, B-complex, iodine, placental extracts, corticosteroids and physiotherapy. They reported a success rate of 62.07% and postulated that, therapies when combined with peripheral vasodilator increased the magnitude of remissions remarkably, while they reduced the treatment duration, dosages of associated drugs and frequencies of relapses. They postulated that the peripheral vasodilator relieves the ischemic effect and helps nutritional and therapeutic measures to reach the affected tissues.⁵⁵

Alternative Medicine

The effects of *immune milk* were tried by Tai YS et al in the treatment of OSMF. Immune milk from cows immunized against a variety of human gut bacteria have IgG type I antibody concentration 20-40 % higher than normal cow milk. In addition it also contains a highly active anti-inflammatory compound that can suppress the experimentally induced inflammation in animal models and can give beneficial effect in patients with rheumatoid arthritis. The authors

reported significant improvement in mouth opening and symptoms among 26 OSMF patients who received immune milk treatment at a dosage of 45 gm twice a day for 3 months along with oral habit intervention.⁵⁶

Physiotherapy

The use of local physiotherapy in the form of forceful mouth opening, and heat has been tried. Heat has been commonly used and the results have been described as satisfactory. Heat has been used in the form of hot rinses, lukewarm water or selective deep heating therapies like short wave or micro wave diathermy. The use of microwave diathermy as one of the physiotherapeutic modality in the management of OSMF was highlighted by Gupta DS et al. The authors used microwave diathermy at 2450 MC/s alone and in combination with injection hydrocortisone, vitamin A and B-complex. The treatment was given daily for 20 minutes at each site of the lesion with 20 to 25 watts of energy. A total of 15 sittings were given. They reported the use of microwave diathermy of much value for moderately advanced stages but very poor and without any satisfactory end result, in very advanced cases.⁵⁶

Surgical Treatment

Surgical treatment is the treatment of choice in patients who have a severe restriction in mouth opening. Different techniques have been tried but the results are not satisfactory as there is contracture of the surgical wound leading to worsening of the condition. The fibrous bands have been surgically excised followed by placement of split thickness skin graft, nasolabial flaps, fresh human placental grafts, pedicled buccal fat pad, oral stent made of acrylic, palatal island flap, or reconstruction using superficial temporal fascia flap and split thickness skin graft.^{57, 58} Surgical excision of the bands using Opus-5 diode laser has shown to result in improvement in mouth opening.⁵⁹

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